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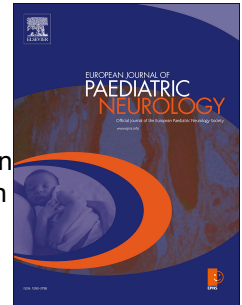
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# Accepted Manuscript

The International Classification of Functioning (ICF) to evaluate deep brain stimulation neuromodulation in childhood dystonia-hyperkinesia informs future clinical & research priorities in a multidisciplinary model of care

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**The International Classification of Functioning (ICF) to evaluate deep brain stimulation neuromodulation in childhood dystonia-hyperkinesia informs future clinical & research priorities in a multidisciplinary model of care**

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**Abstract**

The multidisciplinary team (MDT) approach illustrates how motor classification systems, assessments and outcome measures currently available have been applied to a national cohort of children and young people with dystonia and other hyperkinetic movement disorders (HMD) particularly with a focus on dyskinetic cerebral palsy (CP). The paper is divided in 3 sections. Firstly, we describe the service model adopted by the Complex Motor Disorders Service (CMDS) at Evelina London Children's Hospital and King's College Hospital (ELCH-KCH) for deep brain stimulation. We describe lessons learned from available dystonia studies and discuss/propose ways to measure DBS and other dystonia-related intervention outcomes. We aim to report on current available functional outcome measures as well as some impairment-based assessments that can encourage and generate discussion among movement disorders specialists of different backgrounds regarding choice of the most important areas to be measured after DBS and other interventions for dystonia management. Finally, some

recommendations for multi-centre collaboration in regards to functional clinical outcomes and research methodologies for dystonia-related interventions are proposed.

**Key words**

Childhood dystonia

Hyperkinetic movement disorders (HMD)

Deep Brain Stimulation (DBS)

Multidisciplinary Team (MDT)

International Classification of Functioning (ICF)

CO-OPApproach<sup>TM</sup>

Allied Health Professionals (AHP)

## Background

Objective measurement across all domains of the International Classification of Functioning (ICF), Disability and Health (1) has been recommended as an essential element in rehabilitation (2-4). These include i) body function and structures, ii) activity and iii) participation. Whilst body function and structures focuses on impairments, activity and participation domains include concepts such as capacity and limitations and restrictions. This framework has been widely adopted to define and measure health and disability. It provides common terminology for professionals internationally and from different backgrounds. The focus is on the child and the interaction with two other key domains of the ICF, i) the environment taking into account impairments but also ii) contextual factors such as personal ones. The evaluation of the different dimensions across the ICF allows better representation of the child's needs, strengths and living experience with dystonia with emphasis on family-centred care, the use of functional outcome measures, and measuring how children and young people with disabilities can live meaningful lives.

Despite 15 years since the ICF framework was published, much of the current research in childhood dystonia and other hyperkinetic movement disorders (HMD) has concentrated on genetic diagnoses and other aetiologies. The interventional studies available in childhood dystonia and other HMD focus in the majority on outcomes within the impairment level without attempting to elaborate on what this might mean at the levels of activity and participation (5). A recent Lancet review by Koy et al. (2016) (6) on the management of movement disorders in children outlines a number of recommendations including better trials of interventions, preferably disease-modifying, optimized for different age groups of children and using appropriate assessment scales that can be universally employed across all childhood dystonias from isolated monogenetic, acquired brain injury to hereditary degenerative and neurometabolic causes of childhood dystonia.

Childhood dystonia and other hyperkinetic movement disorders (HMD) are a heterogeneous group in terms of aetiology, motor severity, functional abilities, motor and non-motor co-

morbidities. Dystonia is a neurological syndrome characterised by involuntary, patterned, sustained, or repetitive muscle contractions of opposing muscles, resulting in abnormal twisting body movements and abnormal postures (7, 8) which can also be tremulous.

Dystonia affects adults and children and is one of the most disabling movement disorders, both for the individual and their families. The causes and clinical presentations of dystonia are heterogeneous, and dystonia has mostly been classified by aetiology within two broad categories:

- i. Primary dystonias have no structural brain abnormality and often no known underlying cause, although genetic mutations are being increasingly identified e.g. DYT1; DYT6; DYT11 and many others though genetic heterogeneity and phenotypic pleiotropy is also increasingly recognised (9).
- ii. Secondary dystonias, including Cerebral Palsy (10) in which structural abnormalities of the brain are usually visible arising from perinatal injuries such as periventricular leukomalacia (PVL), hypoxic-ischaemic encephalopathy (HIE), kernicterus, localised strokes of the basal ganglia, cortical and subcortical malformations including hypo- and dys-myelinating disorders and an extremely wide range of individually rare but collectively important neurometabolic disorders as well as neurodegenerative disorders such as Neurodegeneration with Brain Iron Accumulation (NBIA) (6, 7, 11, 12).

More recently, Albanese and colleagues (8) have proposed a new classification based on two axes:

Axis 1: Age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features).

Axis 2: Aetiology, which includes nervous system pathology and inheritance, to “provide meaningful information on any dystonia patient and serve as a basis for the development of research and treatment strategies”.

This classification could be useful in very large cohorts of patients such as an international

database for example as launched by Marks and colleagues (2016) (13). The grouping of all variables into pragmatic, yet clinically appropriate, subgroups might be needed in order to make clinical sense of results across different groups of patients. We have briefly reported (14) the newly proposed classification system to a sample of 145 children and young people presenting with dystonia to a tertiary centre however the application of the classification system resulted in 4 major sub-groups: 1) primary dystonia, ii) primary plus dystonia, iii) secondary static dystonia and iv) hereditary degenerative conditions.

Deep Brain Stimulation (DBS) of the Globus Pallidus has now been established as an effective intervention for primary dystonia, in both controlled (15) and open label studies (16) as well as long term studies (17) and for a general review of DBS in children see Lin 2016 (18-20). In addition, the UK's National Institute for Health and Clinical Excellence (NICE) have approved DBS for parkinsonism (although Parkinsonism is rare in children), dystonia and tremor movement disorders in adults and children and have also provided guidelines supporting the use of DBS as a safe and efficacious procedure for dystonia and tremor (21). Despite these well conceived and described studies, the functional status and recovery of even primary dystonias following DBS has not yet been well-described and young people continue to face significant functional difficulties despite an impressive motor recovery from dystonia impairment, indicating that primary dystonia is a disorder affecting motor function beyond motor skills alone (22). Non-motor symptoms have been described in primary dystonia in the adult population (23-26) but reports in paediatrics are lacking and more research in this area is needed.

There are known to be around 70,000 sufferers of dystonia in the UK alone (27). Although there is evidence of a falling prevalence of CP arising from moderately low birth-weight (MLBW) and very low birth-weight (VLBW) in Europe for the period 1980-2003 with an overall fall in prevalence from 1.9 to 1.77/1000 live births. The prevalence of CP in normal birth-weight (NBW) babies (i.e. the majority of cases) and extremely low birth-weight infants remain unchanged. Also, the prevalence of dyskinetic (dystonic-choreoathetosis) CP has

remained unchanged at 3.5, 4.3 and 4-8% for ELBW, VLBW and MLBW babies respectively and 10.8% for NBW babies (28).

There is also an increasing acceptance that dyskinetic CP is under-recognised in the CP population in general due to lack of appropriate operational definitions of clinical phenomenology with evident consequences for appropriate management (10, 29, 30). The use of the hypertonus assessment tool (HAT) may also help distinguish dystonia from spasticity (31).

Limitations of the standard pharmacological and therapeutic interventions for the management of both primary and secondary childhood dystonias (6, 32) and inexorable progression to functional musculoskeletal deformity within the first 5-10 years of life (33) have therefore resulted in an increasing demand for alternative neuromodulation techniques, such as DBS (6).

Specific studies solely related to the evaluation of outcomes following DBS in childhood dystonia are still limited, particularly as only outcomes on reduction of dystonia are often shared (5) and functional recovery is not well described in the literature (34).

The heterogeneity of this group of conditions makes it difficult to systematically approach measurement across the domains of the ICF, particularly at the level of activity and participation and it requires a multidisciplinary approach including AHPs as part of the core team managing children and young people with dystonia and other HMD. Perhaps this is one of the reasons why research reports regarding functional difficulties and outcomes following interventions are lacking. Even when clinical and objective measures are advocated, scales of dystonia severity alone persist as the sole outcome measure (35) while emphasising that the main goal of rehabilitation is to improve function and reduction of dystonia severity alone may not necessarily result in a change in function. It is therefore critical to review available and valid functional outcome measures on dystonia. The use of outcome measures in childhood dystonia will be addressed later.



The multidisciplinary team (MDT) approach illustrates how motor classification systems, assessments and outcome measures currently available have been applied to a cohort of children and young people with dystonia and other HMD particularly with a focus on cerebral palsy (CP). We aim to report on current available functional outcome measures as well as some impairment-based assessments that can encourage and generate discussion among movement disorders specialists of different backgrounds regarding choosing the most important areas to be measured after DBS and other interventions for dystonia management.

Specific aims of this paper are:

- (1) To describe the Evelina London Children's Hospital & King's College Hospital (ELCH-KCH) DBS service model and explain the process of creating a 'Minimal-acceptable-best practice' model
- (2) To describe what we have learned from dystonia studies and discuss ways to measure DBS outcomes and effects of other interventions for dystonia including the challenges faced in measuring outcomes;
- (3) To suggest recommendations for multi-centre collaboration regarding functional clinical outcomes and research methodologies for interventions with dystonia

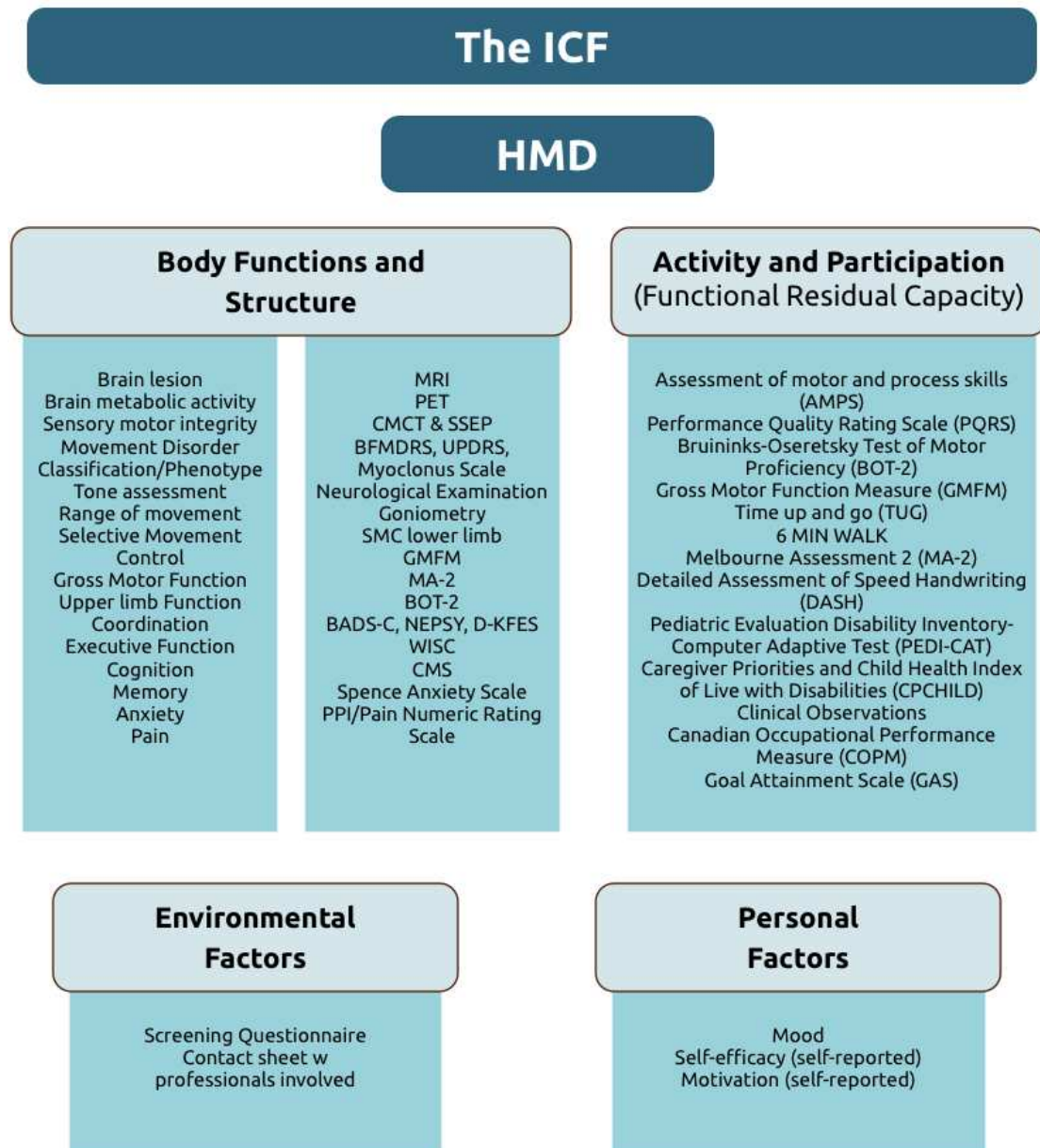
#### **(1) The Complex Motor Disorders Service (CMDS) service model**

The ELCH-KCH DBS service is client-focused and benchmarked to 'best practice' criteria as proposed by the World Health Organisation's International Classification of Function (ICF)

(1). Moving away from impairment-based models of practice, the ICF focuses on *activity* and *participation*. This philosophy forms the basis of our multidisciplinary client-centred service model. Figure 1 shows areas of assessment and intervention in our service model.

Insert figure 1 here

## ICF Areas addressed by the MDT in CMDS



**Figure 1: ICF Areas addressed by the MDT in CMDS.** This figure illustrates the multi-dimensional approach to assessment with examples of some of what outcome measures could be utilised. Not all assessments are completed with all children, as this would depend on their level of motor severity and manual function ability as well as cognitive ability.

**ABBREVIATIONS:** MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; CMCT: Central Motor Conduction Time; SSEP: Somato-Sensory Evoked Potentials; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale (36); GMFM: Gross Motor Function Measure(37); MA-2: Melbourne Assessment – 2(38); BOT-2: Bruininks-Oseretsky Test Of Motor Proficiency (REF); BADS-C: Behavioral assessment of dysexecutive syndrome (39); NEPSY:Developmental NEUROPSYchological Assessment (40); D-KEFS: Delis-Kaplan Executive Function Syndrome(41); WISC: Wechsler Intelligence Scale for Children(42); CMS: Children’s Memory Scale(43); PPI: Pediatric Pain Profile(44); AMPS: Assessment of Motor and Process Skills(45); PQRS: Performance Quality Rating Scale(46); TUG: Time-up and go(47); DASH: Detailed Assessment of Speed Handwriting (48) PEDI-CAT: Pediatric Evaluation Disability Inventory – Computer Adaptive Test(49); CPCHILD: Caregiver Priorities and Child Health Index of Live with Disabilities (50); COPM: Canadian Occupational Performance Measure(51); GAS: Goal Attainment Scale(52); ICF: International Classification of Functioning(1); MDT: Multidisciplinary Team; CMDS: Complex Motor Disorders Service

***How the Evelina London Children's Hospital-King's College Hospital DBS service began.***

The Evelina DBS service was originally created in 2005 after some inspirational work with the Montpellier DBS group. In 2003 and 2004, two children with extremely severe primary idiopathic torsion dystonia (DYT1-positive) were sent from London to Professor Philippe Coubes, neurosurgeon in Montpellier, France. These children were both implanted with bilateral Globus Pallidus Internus (GPi) deep brain stimulators, which resulted in a marked reduction in their dystonia.

The paediatric Complex Motor Disorders Service (CMDS) began in May 2005 with the first bilateral Globus Pallidus Internus (GPi) Deep Brain Stimulation (DBS) implant in a four year-old boy with dystonia secondary to a rapidly progressive neurodegenerative disorder. The functional neurosurgery was performed at King's College Hospital by Mr. Richard Selway, Consultant Functional Neurosurgeon as a joint Guy's & St Thomas' & King's College Hospital collaboration. The appropriateness of DBS in 5 clinically selected children with severe dystonia was discussed with Professor Phillippe Coubes and Dr Laura Cif who visited our unit and advised on clinical issues. These children then became the service's first DBS cases and lead to the successful funding application for a dedicated multidisciplinary Complex Motor Disorders Service (CMDS) by the Guy's and St Thomas' Charity which began recruiting team members of the CMDS at Evelina London Children's Hospital (ELCH) in April 2007. As with all new services, we have received referrals for young people with extreme dystonia at the young adult age-range reflecting the spectrum of unmet need in this field of neurology.

The first stage involved defining a multidisciplinary client-focused CMDS for assessment and management of children and young people undergoing DBS. At this stage, various factors were considered, including listening to the views of children and families being treated, as well as careful consideration of governmental and societal guidelines and recommendations, all of which highlight the need for multidisciplinary team input. These included:

- The National Service Framework (NSF) for Children and Young People (53), whose recommendations include (i) listening to families' feedback in development of services; (ii) promoting social inclusion of children with disabilities and facilitation of improved function and participation in daily life; and (iii) supporting an MDT approach so that services can effectively co-ordinate around the needs of the child and family
- NICE guidelines for 'DBS for tremor and dystonia (excluding Parkinson's disease)' (21), which recommend that DBS intervention and care "...*should be carried out in the context of a multidisciplinary team...*"
- The Dystonia Society UK, which advocates a full MDT assessment process for DBS and regular follow-ups to ensure maximum clinical efficiency (27).

The subsequent NHS approval of DBS for movement disorders (April 2013) with guidance notes was not then available (54).

#### ***Essential components to our assessment and management service model***

The CMDS team at ELCH-KCH consists of a bespoke multidisciplinary team including neurologists, neurosurgeons, a specialist nurse, psychologist, physiotherapist, occupational therapist, speech and language therapist and a therapy assistant crucial to the delivery of a large 'battery' of tests and assessments, video archiving, and consents for assessments working in a trans-disciplinary model of practice to meet the needs of the child (55). One of our main aims has been to move away from a pure medical-surgical model but rather to adopt a family-centred approach reflecting the importance of collaborative partnerships with families, clients and others working with the child.

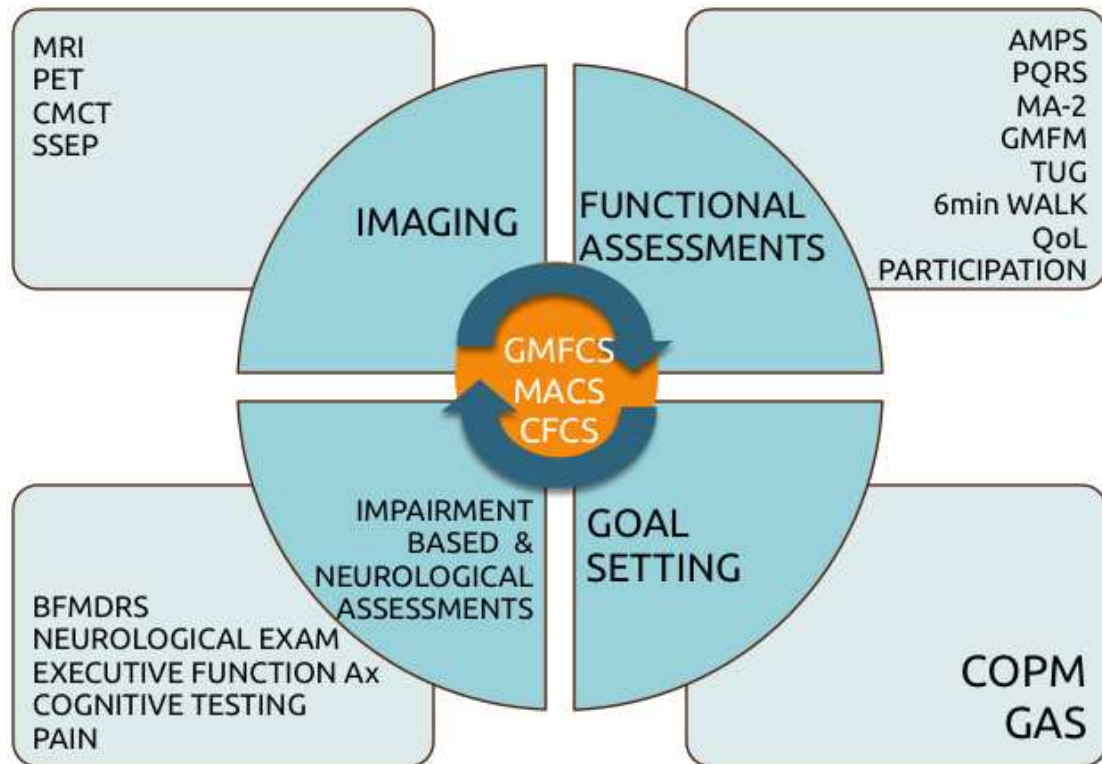
Recently, there has been a shift away from approaches aimed at "fixing" the child/young person, instead, the focus is on activity and participation underpinned by the International Classification of Functioning (ICF). This shift has been driven by factors such as our changing understanding of child development, emphasis on family-centred care, use of functional outcome measures and determining what is important for young people with

disabilities to live meaningful lives. This fosters the children's sense of own competency and enables the young person and their family to address factors that also impact on the child's ability "to do". In short, supporting young people and their families in becoming experts on managing their own condition.

Our assessment process includes a repertoire of imaging and medical testing but goes beyond the impairment level (as outlined in the WHO ICF framework) and also assesses other areas that would affect the child/young person's ability to participate fully in all activities of daily living in the community, albeit within a hospital context.

This multi-disciplinary service has been established to assess the suitability of children with complex motor disorders for specialised neurosurgical interventions such as intrathecal baclofen (ITB) pump implantation for mixed spasticity and dystonia or deep brain stimulation (DBS) for dystonia alone. A number of patients are additionally referred for diagnostic and management support. Patients are referred from all over the United Kingdom and Ireland for DBS and more regionally for ITB. A number of international referrals are received, predominantly for DBS. Figure 2 represents an outline of the assessment process.

Insert figure 2 here



**Figure 2: Assessment Process Outline.** This figure represents the multi-dimensional approach to assessment before a neurosurgical intervention such as deep brain stimulation (DBS) or intrathecal baclofen pump (ITB). The complexity of this model requires the integration and collaboration of a multidisciplinary team.

**ABBREVIATIONS:** MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography, CMCT: Central Motor Conduction Time, SSEP: Somato-Sensory Evoked Potentials, AMPS: Assessment of Motor and Process Skills, PQRS: Performance Quality Rating Scale, MA-2: Melbourne Assessment – 2, GMFM: Gross Motor Function Measure, TUG: Time-up and go, QoL: Quality of Life, BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale, COPM: Canadian Occupational Performance Measure, GAS: Goal Attainment Scale.

### ***The patient journey***

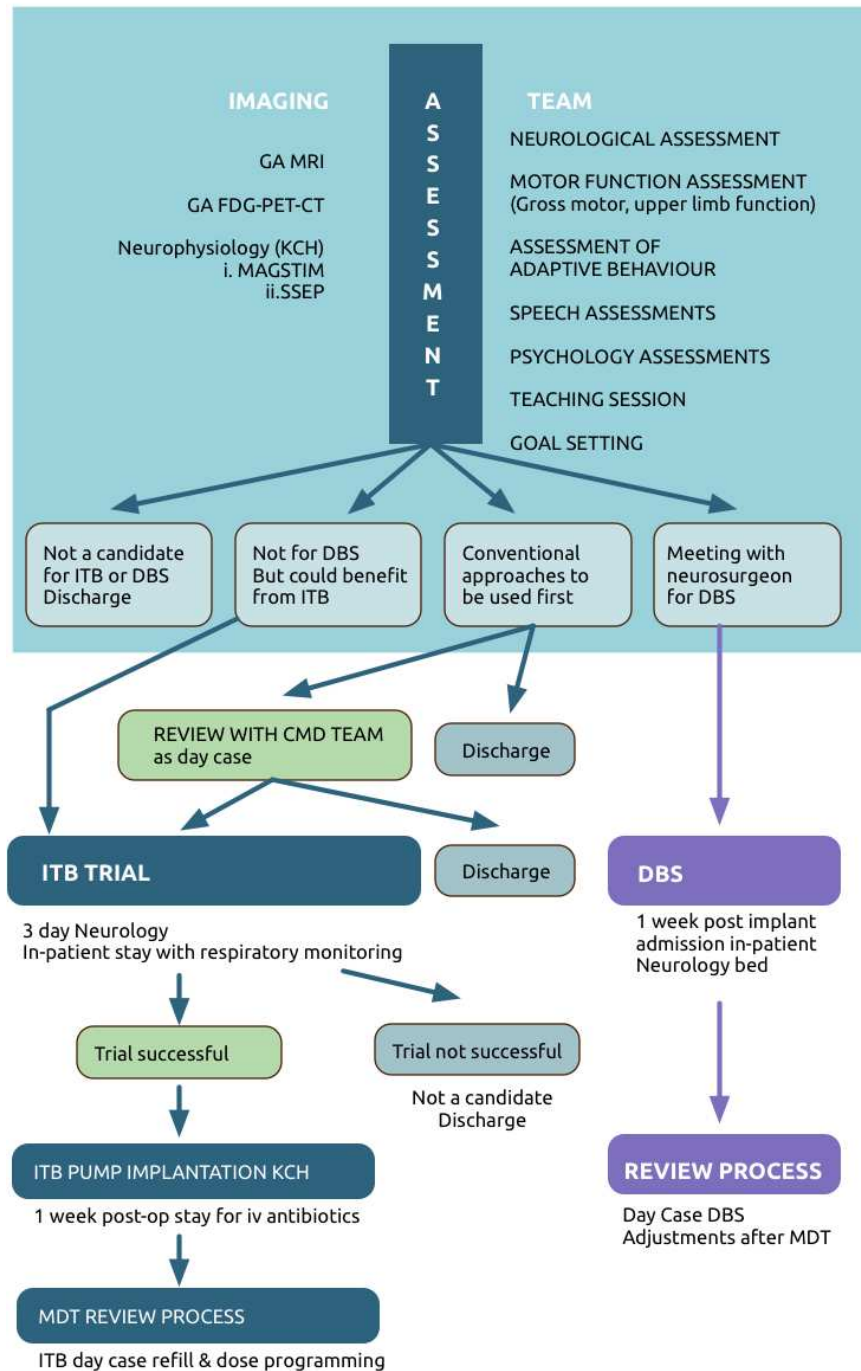
The bespoke multidisciplinary nature of the CMDS is reflected in the patient's journey; from the initial stages of data gathering prior to meeting the child and family, to the final discussions, goal-setting and decision-making for DBS or further management options. The patient journey involves three phases, which are represented in figures 3a and 3b.

Insert figures 3a & 3b here



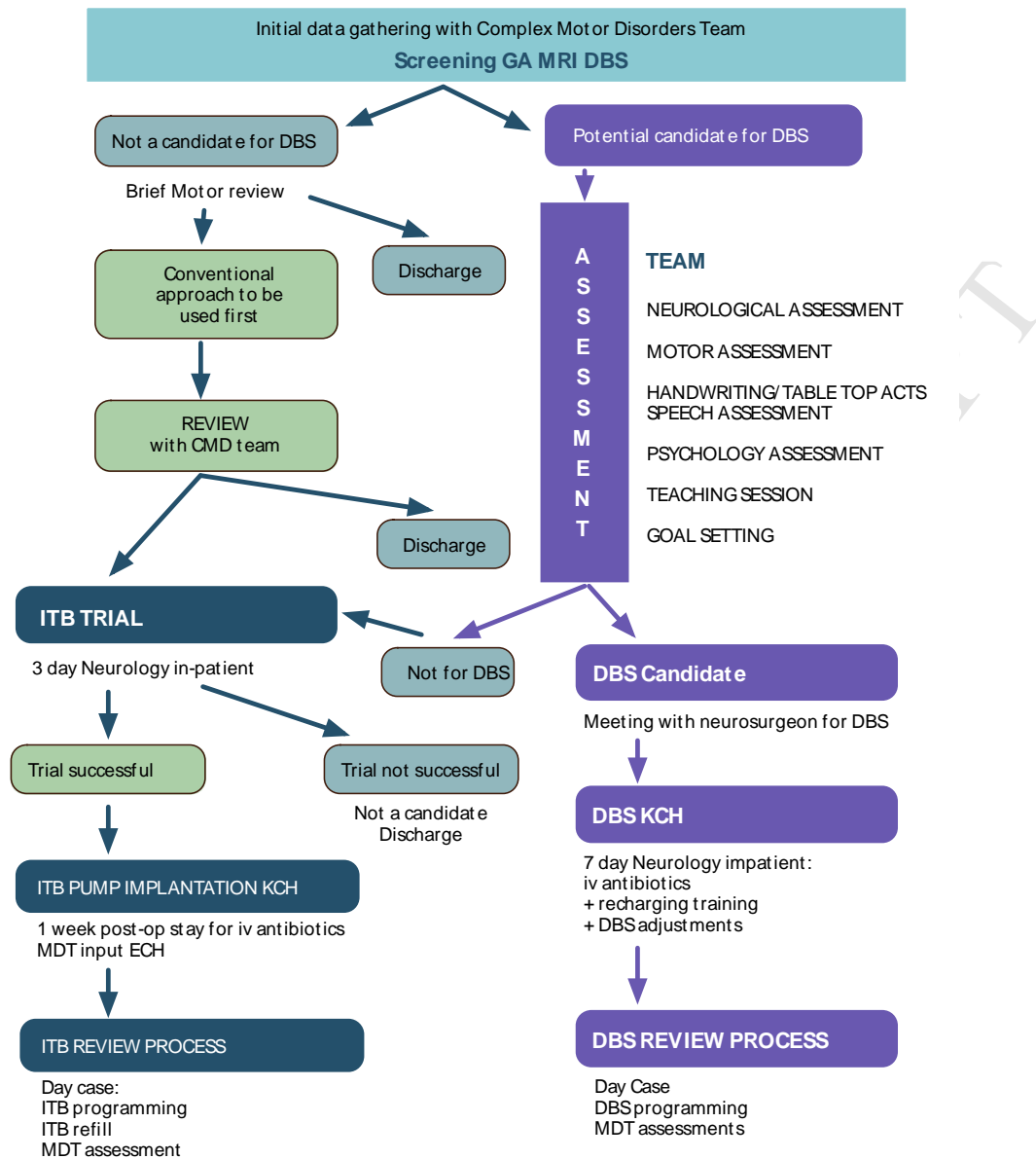
Initial data gathering with Complex Motor Disorders Team

Phase 1: over five separate clinical days



**Figure 3a: Patient Journey over 1 week admission for assessment and decision tree and follow up process.** This figure represents the multi-dimensional approach to assessment before a neurosurgical intervention such as deep brain stimulation (DBS) or intrathecal baclofen pump (ITB) and the decision tree with different phases of assessment, implementation and review.

**ABBREVIATIONS:** GA MRI: General Anesthesia Magnetic Resonance Imaging, GA FDG-PET-CT: General anesthesia F-Fluorodeoxyglucose Positron Emission Tomography-computed tomographic, CMCT: Central Motor Conduction Time, SSEP: Somato-Sensory Evoked Potentials, KCH: King's College Hospital, DBS: Deep Brain Stimulation, ITB: Intrathecal Baclofen, MDT: multidisciplinary team



**Figure 3b. CMDS process over separate hospital visits for assessment and decision tree**

**ABBREVIATIONS:** GA MRI: General Anesthesia Magnetic Resonance Imaging, GA FDG-PET-CT: General anesthesia F-Fluorodeoxyglucose Positron Emission Tomography-computed tomographic, CMCT: Central Motor Conduction Time, SSEP: Somato-Sensory Evoked Potentials, KCH: King's College Hospital, DBS: Deep Brain Stimulation, ITB: Intrathecal Baclofen, MDT: multidisciplinary team.

**Phase 1:** Comprises a full MDT assessment including neuro-radiological and neuro-physiology testing, functional assessments led by allied health professionals (AHP) and a range of impairment-based assessments, quality of life and goal setting.

Phase I can commence (most likely) with a screening clinic run by a consultant neurologist from CMDS and a senior AHP (either physiotherapist or occupational therapist). A whole



week assessment might be preferable for those cases who are rapidly deteriorating or living geographically far from the South East of England. Bearing in mind the capacity of the child and families to endure a whole week of assessments including neuroimaging, neurophysiology and AHP assessments detailed below. This might be further compounded by environmental factors such as bed availability. Before children and families attend their initial appointment a questionnaire is sent which allows gathering of preliminary information about functional concerns and opening a dialogue with family and child/young person. The questionnaires (devised by HG with contributions from other team members) consist of two versions based on the GMFCS severity levels (one questionnaire for GMFCS levels I-III and the other questionnaire for GMFCS levels IV and V). (These are included here as supplementary information – supplementary files 1 and 2). The questionnaires guide clinicians at initial screening regarding appropriate assessments. The family concerns are paramount and are the focus of much of this initial discussion.

The detailed standardised assessments will depend on the functional ability of the young person but as a rule of thumb, the greater the functional ability, the more assessments it will be theoretically possible to complete; the main purpose is to obtain reliable and generalizable measures of function and not be pegged by test-limited ceiling effects. The assessments illustrated in figure 1 encompass assessments for all GMFCS levels but not all will be performed with all the children and young people. On supplementary information (appendices 3 and 4) we have outlined the assessments that are routinely completed by the MDT in all phases of the patient's journey.

The steps in phase one are aimed narrowly at confirming suitability for neuromodulation and more broadly at mapping the *underlying functional residual* capacity of the child. This is set against what we know about the natural history of dystonia in childhood in all the known aetiological categories: i.e. dystonia tends to worsen in 2/3 of cases or stay as bad in a further 1/3 of cases (11); functional deformities become apparent in secondary dystonias around the age of 5 years and then affect 80% of children by age 15 years (33); adverse drug reactions to commonly used antidystonic medication are common (32). This background information

helps families contextualise their child's dystonia preparatory to opting for neuromodulation intervention. The choice of goals clearly reflects a combination of the developmental progress of the child and motor severity across the whole spectrum of motor ability and dystonia severity. One way to describe the aim of neuromodulation is to expand the *functional residual capacity* of the child. This is related to but different from reducing dystonia, because the *functional residual capacity* is activity-related. An often understated aim of the baseline assessment is to help parents, carers and the MDT understand what matters most to the child and demonstrate to families the border-zone between successful and unsuccessful activity as well as those functions which are completely impossible. Goal-setting is explored from the border-zone of function, brought out during the assessment and is therefore clearly applicable to each individual child or young person.

### **Meeting the neurosurgeon and concluding Phase I**

The formal surgical information and discussion meeting is a crucial multidisciplinary team event during which every aspect of the child's case is reviewed, culminating in a review of the imaging, the neurophysiology, the MDT assessment and goals. The purpose here is to review what has already been discussed and allow the neurosurgeon to understand the parent/carer/child perspective(s) in relation to risk and benefit. Surgical risks, including risk of intra-cerebral bleeding leading to possible stroke or fatality (<1% across the literature), device infection, disappointment at lack of efficacy, and a variety of technical complications are reviewed based on published reports as well as our ELCH-KCH data. However we have been able to describe a much lower overall and specific complication rate in our large cohort of children than previously published in smaller cases series, including previously unpublished data for DBS in under 7-year-olds (56). Service-specific risk data is particularly difficult to achieve at the beginning of a service when limited team experience and the absence of a track-record necessitate reliance on published case-series. Broader information spanning all continents may soon be available through the auspices of a international

paediatric DBS registry (PediDBS) (13), aimed at collecting world-wide experience of childhood DBS.

Another important way of helping with decision-making is for families and children to meet others who have been through the service already. Matching by age, aetiology and severity of dystonia is important. Meeting someone after recent DBS and also years later are important contrasting experiences. It is important for these meetings to be independent of the treating MDT. This is often also supplemented by a social media family support group (<https://en-gb.facebook.com/DystoniaSociety/posts/229880783722051>) and advice from the Dystonia Society UK website, including the guide to good clinical practice (27).

A new and important source of information has been our work with parents undertaking this complex decision-making (57) and the work of John Gardner, exploring DBS neuromodulation in children from a social sciences perspective which depicts the implementation of the '*Broad Clinical Gaze*' as a means of defining what is in the child's best interests based on promoting activity and participation (58, 59). As we have discovered, despite categorising our children with dystonia into the aetiological categories of primary or secondary, the actual efficacy of DBS for each specific child remains uncertain, in part because wide variations in responsiveness within each aetiological grouping is possible. Bridging the gap between published cohort and specific patient outcomes requires clinical experience and patience and the need to explicitly discuss 'disappointment' as a possible complication of DBS surgery. Further detailed information on how DBS works has been recently reviewed (6, 18, 19, 60, 61). Overall, honesty and candour still remain the best tools in the toolbox when facing these issues with the family together with the neurosurgeon.

**Phase 2** includes the DBS surgery and peri-operative care.

Our neurosurgical practice has been previously described in detail (62-65) and with a few exceptions involves bilateral in-frame stereotactic targeting of the postero-infero-ventrolateral globus pallidus internus under inhaled isoflurane general anaesthesia preceded by a once-a-day Octenase total body head-toe shampoo for 5 days before DBS and 5 days of

perioperative cefuroxime iv antibiotics TDS for prophylactic infection reduction beginning with induction of anaesthesia at the start of DBS surgery. A single pass microelectrode recording is used to assess the ideal depth of the stimulating intracerebral electrode (62). Planned recovery from DBS surgery includes a nurse-controlled morphine infusion for up to 24 hours post-operatively together with Ondansetron anti-emetic 8-hourly i.v. until nausea subsides. All regular anti-dystonia medication is usually restored on waking up from anaesthesia.

**Phase 3** involves post-operative multidisciplinary reviews at regular intervals of 1,2,3,6,9,12 months and 6 monthly thereafter, both to monitor outcome and progress and for the MDT to work collaboratively with the family in order to ensure good neurostimulator recharging routines and maximise the effects of DBS on the young person's functioning and participation in daily life. Usually, a BFMDRS test is performed at each visit along with a Timed Up and Go test (TUG) and six-minute walk, when appropriate. The majority of functional outcome measures take place are at 1, 2 and 5 years post DBS, though annual full MDT assessments would be the ideal to capture waxing and waning efficacy of DBS across the group, particularly in the light of recent information describing apparently on-going improvements in dystonia for each year of neuromodulation (66) rather than outcome saturation after the first year of DBS. Reviews are repeated sooner if clinically indicated.

## **2. What we have learned from dystonia studies. An outline of functional clinical outcomes proposed (and open for discussion)**

A recent scoping review on the pharmacological and neurosurgical interventions available for dystonia and other HMD revealed 72 management strategies (include anticholinergic medication) all failed to address what mattered most to children and young people. For the majority of the interventional studies, the primary outcome measure was an impairment measure (5), most often, the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (67) though Liow et al 2016, using the ICF-framework of functions and Dystonia Severity

Assessment Plan (DSAP) have shown that dystonia may respond well to Gabapentin (68) particularly if associated with pain, difficulty tolerating seating and poor sleep.

More recently Koy et al 2016 (6) reviewed ‘advances in the management of movement disorders in children’ and it has been concluded that therapeutic options for children with dystonia remain an unmet need.

A systematic review (69) on interventions for cerebral palsy (CP) only provided evidence of interventions for spastic CP without specific reference to dyskinetic CP. To date, no studies exist of non-medical/non-surgical interventions based on activity and participation in children with dyskinetic CP or any other HMD or even of specific sub-analysis of dyskinetic CP results within studies that might have included a few cases within larger spastic CP cohorts. Therefore generalisations of results in this population should be taken with caution.

In this section we outline some key messages from the different studies currently available.

This section is divided into different ICF domains:

- i) **At the level of impairment.** We particularly focus on assessment of dystonia severity, gross motor and upper limb function, assessment of cognition and executive function impairments and other non-motor components and finally evaluation of pain and sleep.
- ii) **At the level of activity and participation** we briefly describe the classification of functional abilities applied to dystonia and the evaluation of mobility, abilities in daily life activities and adaptive skills. We also include in this section some detail outline of goal-setting and objective evaluation of the goals.
- iii) **Assessment of quality of life.** Even though quality of life (QoL) is not an area that is measured by the ICF, this is an important area to measure in childhood disability.

We acknowledge that there are also personal and contextual factors to consider and these are not discussed here as the knowledge of the influence of these factors is even less well-understood. However we have also collected measurements of carer burden.

Given the lack of reports using functional outcome measures across different multidisciplinary teams, this guideline serves as a preliminary discussion point.

Table 1 summarizes the strengths and challenges of impairment scales such as the BFMDRS and of functional outcome measures.

Insert table 1 here

*Table 1: Challenges and Strengths of functional outcome measures vs the Burke-Fahn –Marsden Dystonia Rating Scale.*

<b>BFMDRS – STRENGTHS</b> Wide-spread use as a DBS outcome measure Systematic and structured evaluation Proven validity and reliability in adult primary dystonia No expensive resources required – relative ease of use Can be scored by a range of professionals Allows analysis of outcomes related to specific items Numerical result allows comparison over time within and between subjects Can be used in both paediatric and adult cases allowing continued use after transition.	<b>FUNCTIONAL OUTCOMES - STRENGTHS</b> Intended for use in a paediatric (+/- adult) population. Measure skills relevant to daily life More likely to measure items that are meaningful to children and carers Useful tools to inform realistic goal setting Adds to understanding of impact of DBS on function and daily life Proven reliability Numerical result allows comparison over time within and between subjects
<b>BFMDRS – CHALLENGES</b> No validation or reliability studies in paediatric population May require further validation for secondary dystonias Floor effects for more involved children Scoring criteria not adequately described Disability scale too crude Scores dystonia, not function or other impairments Non interpretive use of the movement scale may result in high scores despite little dystonia Functional outcome changes do not always correlate to similar trend in BFM score Potential Moving and Handling risks Requires cooperation and degree of cognition	<b>FUNCTIONAL OUTCOMES-CHALLENGES</b> Significant clinical time required to implement and score Specialist skills/training required for some measures Resource intensive Discipline specific Implementation challenges: - application difficult in highly disabled individuals - variable ability - unable to apply all measures to all cases - impacts on between subject cohort comparison Not all are validated for use in dystonic movement disorders Paediatric v adult measures – change in measures used at transition Require cooperation and degree of cognition

*BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale, DBS: Deep Brain Stimulation*

## **2.1 At the level of body function and structures. Level of impairment:**

### **2.1.1. Assessment of motor impairment:**

#### **Dystonia Severity**

The BFMDRS rates dystonia severity and was originally developed in adults with primary dystonia though it has been applied almost systematically to children with secondary dystonia including dyskinetic CP and hereditary degenerative conditions such as PANK-2 disorders. There have been several reports exploring the sensitivity of this measure by comparing the results with other measures of activity and participation (70-72) and goal attainment using the Canadian occupational performance measure (COPM) (70) and goal attainment scale (GAS) (72). Results in secondary dystonia show improvement in goal acquisition despite little change in dystonia severity as measured by the BFMDRS, partly because the scale magnifies the benefit of small changes to dystonia at the mild end of the dystonia spectrum compared to the severe end. For instance a 10 point change to someone with a baseline BFMDRS of 20 results in a 50% improvement in dystonia. On the other hand, a 10-point change in BFMDRS to someone with a baseline of 100 gives only a 10% change. This has led to the question: ‘to whom does a 10-point change in BFMDRS matter most?’ Another way of looking at this is to consider the idea of ‘Functional Residual Capacity’ defined as [maximum BFMDRS-baseline BFMDRS]. Using this, a mildly affected subject with a baseline BFMDRS of 20-points retains a large amount of “Functional Residual Capacity” which does not change much after a 10-point change. However, the subject with a baseline BFMDRS of 100 experiences a functional capacity gain of 50% after a 10-point drop in BFMDRS. Such considerations are leading to the use of absolute rather than relative changes in BFMDRS scores respectively. Further, preliminary analysis of the results using a blind-rated standardised outcome measure, the assessment of motor and process skills (AMPS) (45), are promising in showing significant, clinically important changes with an objective, blind-rated measure of functional ability despite relatively little BFMDRS change (22). Other impairment rating scales including those that differentiate between dystonia and choreoathetosis, the dyskinetic impairment scale (DIS) (73) have been proposed. Until now, no interventional studies using

DIS as a primary outcome measure exist to explore the feasibility of applying and scoring this for clinical purposes. However, the DIS does show that the dystonia component of the DIS contributes far more to disability than the chorea component of the DIS (74). This may explain why BFMDRS scores may remain elevated because of persistent choreoathetosis at rest and during activity maintains an elevated score even though the dystonic element may have diminished substantially.

Published clinical findings are mainly limited to the neurological impairment. Given the heterogeneity of our sample, the validation of this scale in primary adult dystonia (36) or in a multicentre trial also with adult primary dystonia (mean age 51 (SD 14.8)) (75) might be challenged when applied to a group of secondary dystonias such as dyskinetic CP. Reviewing dystonia in children in 2013, Mink highlights the lack of a perfect dystonia rating skill that has shown sound psychometric properties across all types of dystonia in childhood (76). This problem has now been partly overcome using a 'Rosetta Stone' method which 'translates' the BFMDRS impairment scale into three functional scales commonly used in CP classification for a group of primary, secondary (including CP) and progressive dystonias of childhood (67). The three functional scales have been used and validated in the world of cerebral palsy research (77) and comprise of i) the gross motor function classification system (GMFCS) (78), ii) the manual ability classification system (MACS) (79) and iii) the Communication Function Classification System (CFCSS) (80).

### **Gross motor severity: using the GMFM**

Some assessments of gross motor function have been classified under the ICF across more than one domain such as the gross motor function measure (GMFM) (37) which crosses body function and activity domains. To our knowledge, no systematic way of assessing the outcomes of interventions in dystonia exist using standardised assessments of gross motor function. Preliminary results using GMFM before and after DBS (81) have now been extended to a larger cohort of children and young people and this work will soon be available in the academic literature.



### **Upper limb severity: the QUEST and MA-2**

Similarly to the GMFM, measures of upper limb function often move across two domains of the ICF such as impairment and activity. This is the case for the Quality of Upper Extremity Skills Test (QUEST) (82) and the Melbourne Assessment 2 (MA-2) (83). Both assessments have been used in the measurement of the medical and surgical interventions (71, 84). The MA-2 assessment, for example, was improved from the original Melbourne upper limb assessment (85) with only 1 dyskinetic CP in the sample of children used to test psychometric properties of this UL tool. We are currently leading a validation process of the assessment using the MA-2 and establishing inter-rater and intra-rater reliability for dystonia in childhood. Whilst some established teams might have initiated measuring upper limb function using the original Melbourne, the authors have produced guidelines so that the scores can be extrapolated and used in the updated version of MA-2. This has advantages and might provide a better understanding of the difficulties that children and young people experience given that the MA-2 measures 4 distinct areas including: 1.Range, 2.Accuracy, 3.Dexterity and 4.Fluency of movement (ROM) respectively. The combination of results from MA-2 and comparison with other outcome measures in dystonia could prove an interesting advance in the understanding of changes through interventions such as DBS. For example, one could hypothesise that changes in ROM for children without contractures and deformities might reflect a change in sustained postures (dystonia) whilst changes in dexterity and fluency might refer to a more phasic element of the disorder (rapid dystonia, choreoathetosis or tremor).

There are other established upper limb assessments used such as the Assisting Hand Assessment (AHA) (86) or questionnaire-based Children Hand Use Questionnaire (CHEQ) (87) but these are tools to be used with children with unilateral involvement. Given that the highest proportion of dyskinetic CP include children with 4-limb involvement, tools such as AHA or CHEQ are not likely to be assessments widely adopted in the teams evaluating interventions such as DBS or ITB. Application of these tools to children and young people with asymmetric bilateral upper limb involvement should not be encouraged.

### **Upper limb assessment using kinematics**

Advancement in this area has been made in the last few years measuring upper limb movements using kinematics by a few groups (88-92). However, the use of kinematics in combination with other functional assessments to evaluate intervention outcomes is yet to be performed and kinematic impairment variables need to be analysed using principal component analysis to provide a 'numerical snapshot' for comparative and analytic purposes and then translated into a meaningful functional score.

### **Quality of movement and selective movement control**

Quality of movement can be measured using the Quality Function Measure (QFM) (93). The QFM has been applied to a small sample of children and young people with dystonia and other HMD (94) in our centre, exploring the psychometric properties of the tool when applied to this heterogeneous group of children. The measure might be sensitive enough to capture changes following DBS for example. Changes in QFM could be correlated to other measures of gross motor function such as the GMFM as well as more functional measures across the domain of activities and participation such as the AMPS or Mobility assessments.

The objective assessment of selective movement control (SMC) offers the clinician information about why a child might have functional difficulties, since dystonia alone might not be the only contributor to functional difficulties. Although assessment of SMC for the lower limb is routinely performed using standardised assessments, uptake of the SMC assessment for the upper limbs is scarce.

### **2.1.2. Assessment of non-motor components in dystonia:**

In both the cerebral palsy and the dystonia literature, the focus on motor impairments dominate over non-motor components such as cognition and executive function. However, there are some interesting reports and studies focusing on non-motor factors, particularly in the adult population with dystonia (24-26, 95).

### Assessment of cognition

Reports have focussed on cognitive function in children with spastic CP (96) however Pueyo and colleagues compare children with spastic and dyskinetic CP (97) albeit only a small sample of dyskinetic CP and the classification is unclear (i.e. Dyskinetic diplegia). More specifically, there are now two relatively large sample reports for cognition stability before and after DBS in primary childhood onset dystonia (98) and secondary paediatric dystonia (99) and in a small group of Pantothenate Kinase Associated Neurodegeneration (PKAN) dystonia (100). Owen and colleagues (2016) report an improvement on perceptual reasoning following DBS in secondary dystonia (99) and Mahoney (2011) reported improvements in tasks with a visual content such as picture concepts; vocabulary/picture vocabulary; visual immediate and delayed memory; faces immediate and delayed memory (100). Although these reports are promising, more work in this area is encouraged including the elimination of possible confounding variables and the role they might play in the improvement. Improvements noted in cognition could be due to several factors such as i) a reduction of medication after DBS, in cases of dystonia and other HMD, ii) improved motor ability to access tools and materials such as reduction of a dystonic neck pull that allows the child to keep the head in the mid-line for eye-gaze access (an improvement that the BFMDRS is unlikely to be sensitive enough to detect) and iii) the DBS has an independent effect on cognition by directly influencing the cognitive-associative basal ganglia-cortical loop.

There are certainly challenges to measure cognition in this heterogeneous population, which comprise all levels of GFMCS, MACS and CFCS. Some children and young people are verbal whilst others can only communicate via eye-pointing for example. Manual Function will have an impact on what tests can be performed by the child and it is important that children and young people are not penalised for their movement disorder when they are attempting to access materials and tools for cognitive assessments. Unfortunately, there is probably no single measure that can be applied to the entire cohort with dystonia though an attempt should be made to assess our most severely affected children. In our group the joint work between psychology and occupational therapy has allowed some assessments to be

completed with children and young people that are both non-verbal and GFMCS level-V and who only have reliable eye pointing if they are handled outwith their wheelchair (e.g. on the lap) by their parents or an experienced therapist. We have attempted to maintain the therapist bias-free when interpreting eye movements whilst handling children by positioning the materials away from the therapist so that she/he cannot see what the answers are. We are in the process of describing in detail the practicalities of applying this approach to enable children to access psychological testing.

### **Assessment of executive function**

The assessment of executive functions in childhood dystonia and their contribution to the understanding of baseline characteristics/profile has not been widely reported. In fact, this is an aspect that has not been widely studied even for children with spastic CP although some more reports are emerging (96, 101-104). The Behavior Rating Inventory of Executive Function (BRIEF) (105) is a parent-reported questionnaire but correlations with objective executive function scores/tests of assessments of adaptive skills are not yet available. Given the non-motor factors reported in the adult dystonia literature, it seems reasonable to measure this in childhood-related dystonia disorders. Again, as with cognitive assessments, the heterogeneity of the children and young people attending our service poses difficulties in terms of choosing only one assessment, so a core set of assessments should be considered depending on the motor-capacity of the child. We propose that these core sets of assessments are grouped not only on verbal or non-verbal capacity but also in relation to MACS and CFCS levels as they might serve as indicators of access-limitation to materials (many requiring manual function to use pen and paper).

Motor-planning defines how a motor goal will be achieved (106). Steenbergen and colleagues have investigated motor-planning deficits in congenital hemiplegia as a possible underlying reason for difficulties in activities of daily living (ADL) (107, 108). Others have also investigated motor-planning ability in children with unilateral involvement (107, 109, 110)

and concluded that there was no relationship with functional ability though the latter was only measured by a questionnaire. These studies have been performed in spastic unilateral cerebral palsy. Although clinically many of the same issues might be present when assessing ADLs performed in dystonia, the pathophysiology of unilateral spastic CP and dystonic CP (or any other dystonia) is very different. In fact, the same group of authors recommend future rehabilitation efforts to be guided by treatment efficacy with specific pathophysiology (111). In our experience, there seems to be a significant element of motor planning which influences a child's ability to perform ADLs but clearly the pathophysiology will be different to current available studies and we urge caution using recommendations taken from studies of spastic CP. A very recent report by Kukee and colleagues (2016) studied 11 children with hemidystonia (and some spasticity) using kinematics and concluded that the reduced coordination during movement could reflect deficits in motor planning (88). The possibility of visuospatial orientation (mental rotation) abnormalities in dystonic children also require evaluation when interpreting processing skills in dystonia.

### **Assessment of Anxiety**

Reported in the adult primary dystonia literature (95), anxiety is a common feature observed in children and young people with dystonia attending our clinics. With some limited evidence on behavioral interventions in primary dystonia (23) there are currently no studies available in childhood dystonia.

### **Assessment of Pain**

Pain is one of the most frequently reported areas of concerns by young people with dystonia and their families (5, 34) and improvements in dystonia pain have been recently reported with gabapentin (68). Pain is also a frequently reported concern for children with CP (112-114). Reduction of pain is possible with DBS even though significant changes might not be captured in terms of dystonia reduction (72). There are several pain assessments in use but again, the use of only one assessment for all children and young people might prove difficult

as some need the child to directly respond either verbally or using eye pointing (VAS) (115) and others might need to be used as a proxy measure by parents if the child is non-verbal or either too young or cognitively not able to provide a reliable answer such as the pediatric pain profile (PPP) (44). As pain reduction has been one of the most frequent goals identified by young people and their families in our cohort (5, 34), we have been able to use the COPM to measure changes in pain affecting daily life. The COPM can be used with all children and young people and their families and may be used to rate pain if this is a goal for intervention and it affects any day-to-day activities. More information is detailed in the goal-setting section below.

### **Assessment of Sleep**

Sleep forms an essential component of health and well-being and is characteristically fragmented throughout life in children with dystonia. The Dystonia Severity Assessment Plan (DSAP: 'dystonia soon as possible') (116, 117) is based on two critical observations of wellbeing in dystonia of childhood: the ability to sit comfortably and sleep well at night (DSAP grade 1). Poor sitting tolerance but preserved sleep quality and quantity lowers the DSAP to grade 2. An inability to sit comfortably or sleep at night constitutes the need for urgent clinical review: DSAP grade 3 and may herald the rapid deterioration to metabolic decompensation (DSAP grade 4) and status dystonicus (DSAP grade 5) in short order. We have begun to use the DSAP to monitor the progress of children with severe, often brittle dystonia and measure improvements after gabapentin (68) along with the ICF domain on sleep: 'Amount of sleep' (B1340): 'Maintenance of sleep' (B1342) graded 0-4 where 0=no impairment/difficulty; 1= Mild impairment/difficulty (present <25% of the time, intensity is tolerable, rare); 2= Moderate impairment/difficulty (present <50% of the time, intensity is interfering in day-to-day life, occasional); 3= Severe impairment/difficulty (present >50% of the time, intensity partially disruptive, often); 4= Complete impairment/difficulty (present >95% of the time, intensity totally disruptive, constant); 8= Not specified (insufficient information); 9=Not applicable

Such assessments of sleep are important because of the beneficial impact of sleep in

‘switching off dystonia and chorea’ (118-120).

### **2.1.3. At the levels of activity and Participation:**

#### **Classification of function**

Well-established classifications of functional ability for gross motor (GMFCS) and manual function (MACS) are being used in studies of cerebral palsy. The use of these classifications in childhood dystonia studies (even when including dyskinetic CP) is less usual. We recently looked at the use of these two classification systems and included a more recent one classifying communication (CFCS) with childhood dystonia (both dyskinetic CP and other forms of childhood dystonia and other HMD) using a ‘Rosetta Stone’ approach, i.e. correlating the BFMDRS with the three motor function scales (67). The correlations between GMFCS and BFMDRS showed a clear linear relationship indicating almost equal blocks of 20-25 BFMDRS points between each of the GMFCS levels. It could be argued that even for studies that are not describing the GMFCS levels, one could take the BFMDRS Movement Score and have an approximate idea of how functionally impaired the children in those studies might have been. Although correlations were high, the relationship between MACS and CFCS with the BFMDRS did not show such a clear linear relationship in the milder categories I, II and III, possibly indicating that a child’s ability to access communication and to perform ADLs is not purely down to motor but also that non-motor factors such as cognition or planning might have an important role. We recommend a minimal dataset for future studies to classify children and young people using these free, easy and quickly applied functional classifications so that comparison between populations and cohorts from different studies is possible.

#### **Evaluation of abilities in daily life activities, adaptive skills**

Since the literature is predominantly concerned with the domains of body structure and function, there is limited understanding of either functional characteristics of children and

young people with dystonia and other HMD or of interventions to improve areas of daily life activities or 'adaptive skills' (5).

'Adaptive skill's or 'adaptive behavior' include age-appropriate skills necessary to live independently. Often measured with questionnaires such as the Pediatric Evaluation Disability Inventory Computer Adaptive Test (PEDI-CAT) (121), the Vineland Adaptive Behavior Scales (Vineland-II) (122) or the Adaptive Behavior Assessment System (ABAS-II) (123). In childhood onset dystonia and other HMD, the use of these assessments has not yet been formally used. In one study using the PEDI, Öhrvall and colleagues explored the relationship between self-care and mobility skills and the MACS levels. They suggest a clear tendency for functional skills to increase with age and discuss the age at which different MACS levels are likely to achieve top scores on the PEDI. At age 9 with a MACS I and at age 12 with a MACS II compared to typical developing children aged 6 years 6 months (124). These recommendations whilst useful as a potential predictor might not hold when applied to children with dystonia other HMD including dyskinetic CP. For example, in the above study, the children with dyskinetic CP were all classified MACS III-V. Caution therefore should be taken when applying research results that are mainly based on spastic CP to children and young people with dyskinetic CP. The use of this relatively inexpensive assessment across different centres, together with MACS and GMFCS classifications could provide us with large enough numbers to explore the relationship between these classifications systems and the PEDI-CAT.

An objective assessment that focuses on activities of daily living is the Assessment of Motor and Process Skills (AMPS) (45). Better understanding of motor and non-motor baseline characteristics of children and young people with HMD would aid us in developing more targeted interventions in our cohort of children. Preliminary evidence using AMPS pre- and post-DBS is available (22).

One issue remains in finding an appropriate outcome measure that could be applied to such a heterogeneous population with different levels of motor severity, pathophysiology and functional ability. However, given that the focus and priorities of children and young people



and their families revolve around every day activities, there is a need for measuring outcomes around this domain.

Our assessment process includes a repertoire of imaging and medical testing but goes beyond the impairment level (as outlined in the WHO ICF framework) and also assesses other areas that could influence the child/young person's ability to participate fully in all activities of daily living and in the community.

The extent to which outcome measures generate future goals will be explored.

#### **2.1.4. Goal-setting in dystonia**

Finding out the real priorities and concerns for young people with movement disorders such as dystonia, particularly those that undergo DBS, will enhance our knowledge of what is really important for these young people and how we can help address those areas of concern and need. Tools, such as the Canadian Occupational Performance Measure (COPM) (51) and the Goal Attainment Scale (GAS) (52), directly identify and measure client/carer concerns and the extent to which the intervention has led to meaningful change in these areas. These tools provide a meaningful way of measuring how well we are able to pre-operatively predict an individual's response to DBS, which is useful in informing future client selection, as well as identifying goal areas more likely to be responsive to the intervention. Such a model is applicable to a range of interventions and is widespread in paediatric practice, which we consider an *essential benchmark* for the delivery of a complex motor disorder service for children and young people offering invasive interventions such as DBS.

The implementation of formal goal-setting for DBS therapy, using the COPM, over a period of some years has made it possible for our service's therapists to counsel parents about DBS results based on therapist experience with a cohort of more than 130 children implanted since 2007. For instance, our accumulated experience indicates frequently positive outcomes with regards to pain and comfort but typically little response in terms of speech intelligibility in children with secondary dystonia.

There have been a number of challenges to embedding current goal-setting practice. Occupational therapists and physiotherapists need to comprehensively evaluate the child in order to determine the primary impairments contributing to the functional difficulties and the extent to which the intervention (DBS) may address these. For example, impairments commonly seen in association with dystonia in our patient group include hypotonia, reduced selective motor control, contracture and deformity, and planning and organisational difficulties, yet DBS would not directly address all these aspects, except in the sense that dystonia comprises both hypertonia and hypotonia i.e. both extremes of tone and posture range and DBS stabilises the lurching of the motor system from one extreme to another. The possibility of fluctuating mood, behaviour or even cognitive functions in dystonia in childhood requires further exploration. The challenge is to identify which areas may reasonably be expected to improve should DBS successfully ameliorate involuntary postures and movements and how those will influence function and participation. We have found it useful to defer formal goal-setting until the end of the assessment process, allowing a more comprehensive picture to be built-up between family and allied health professionals regarding the factors contributing to the child's functional difficulties and a good rapport has been established to allow for honest, open discussions about expectations on both sides.

Parents and carers will often identify an impairment area and need prompting to identify the related functional difficulty. For example, a parent may initially state that their goal would be for their child to move less, while with prompting may identify that reducing involuntary movements would allow their child to be safely placed on an adapted toilet seat for toileting or to safely spend leisure time on the sofa with siblings. In this way, the aim is to demonstrate the extent to which reduction in dystonia and dyskinesia through neuromodulation positively improves day-to-day activities the child and family identify as important. Describing a specific functional concern is also easier to quantify than the subjective reporting of improvement or deterioration in involuntary movements.

In practice, it can be time consuming to formally document goals and agree means by which progress in goal-areas will be measured. This is particularly an issue at the initial goal-setting episode, as the pre-operative semi-structured COPM interview may typically take an hour or more, albeit with substantial variations. We think this time is fully justified and manageable given the importance in capturing ‘what matters most’ and what would constitute an improvement, *before* proceeding to DBS implantation.

Follow-up evaluations are less time consuming. We have found the clear qualitative descriptions of areas of concern can serve as very useful prompts during feedback and as useful reminders of a child’s state some time previously when parental recall may not be reliable. For example, when asked how an area such as sleep has changed, a parent may say the situation is unchanged, yet the child may be described as now waking only once a night for a drink in contrast to parents being up 5-6 times a night for protracted periods due to painful dystonic spasms. In this way, the goal-setting process helps both families and professionals to remain focused on the areas that were identified as concerns prior to surgery providing clarity on the extent to which meaningful progress has been made.

We have noted cultural, emotional and personality influences in the COPM scoring process. For example, a parent may describe an area presenting significant care difficulty and rate poor performance for this concern, but not overtly express dissatisfaction with the problems they experience as they consider it their “duty” to meet their child’s needs.

Goal-setting in progressive neurodegenerative disorders, such as pantothenate kinase neurodegeneration (PKAN), has proven particularly challenging and formal goal-setting tools such as the COPM may not be appropriate in all cases. In these conditions, positive progress may be only briefly achieved for 1-2 years, but stability or a change in the rate (profile) of deterioration may represent successful intervention. Further, with time, the inevitable and inexorable deterioration can make it difficult to ascertain the extent to which DBS is

significantly ameliorating the child's movement disorder and improving the child's quality of life. We have had experience in some PKAN cases, where the young person has rapidly gone into status dystonicus following inadvertent de-activation of the DBS, which resolved quickly with reactivation. Such experiences have highlighted to both families and clinicians the extent to which DBS may be positively contributing to a child's management, despite the persistent and severe dystonia, which may be present when the DBS is active. Clearly, it would not be ethical, nor desirable, to inactivate DBS to evaluate efficacy, particularly given concerns of precipitating status dystonicus as a rebound phenomenon following DBS cessation (116).

#### **Objective and blind rating evaluation of goals:**

##### **PQRS**

As Mink (2013) points out, movement disorders in childhood are a heterogeneous group and there are challenges not only with definition of their diagnosis but also with assessment and treatment (management) across different aetiological background, motor severity and age (76).

As with other populations, the use of goal-setting has been proven possible and sensitive to capture change following surgical interventions (70, 125) but one argument would be that goal-acquisition reporting with tools such as the COPM is a self-reported outcome and therefore lacks the objectivity that many claim necessary for the systematic evaluation of interventional outcomes. With the challenges of applying the same assessment across this heterogeneous population, the use of client-centred and client-chosen goals is promising. The objective evaluation of those goals is possible and has been tested in studies using a specific intervention named cognitive orientation to daily occupational performance (CO-OP) (126-129). Using the Performance Quality Rating Scale (PQRS) (46) it is indeed possible to objectively measure client-selected functional goals. A study validating the use of PQRS for dystonia and other HMD is currently in progress (130). This is a promising tool that would allow a systematic study of objective measurement of goal acquisition and comparison with

self-rated goals from the children and families perspective. It could be used across any age, GMFCS, MACS or CFCS level and across any aetiological background.

#### **2.1.5. Assessment of quality of life**

Quality of life (QoL) is not yet included in the ICF and is often considered separately. Often used as an outcome for research studies in cerebral palsy (131) and in adult movement disorders. In childhood dystonia, Eggink et al. 2014 recently reported the health related quality of life (HRQOL) in rare inborn errors of metabolism with movement disorders (132). QoL is self-reported and it can be used towards studying health economics calculations. HRQOL questionnaires are self-reported and can be easy and quick to administer. Cost effectiveness of a study can therefore be calculated using cost per quality-adjusted life years (QALYs) where possible. For example, the EQ-5D-5L (133) is a generic, preference based, HRQOL that has 3 versions, making it possible to apply independently of the age; EQ-5D-Y (for children under the age of 12), EQ-5D-3L (for young people aged 12-18) and EQ-5D-5L (for young adults and adults).

#### **2.2. Can we learn from studies of dystonia in adults or from studies of CP?**

When evaluating treatment interventions with childhood onset dystonia and other HMD, the evidence other than pharmacological or neurosurgical is scarce and disappointing. From Novak's review in 2013, the non-pharmacological/surgical interventions that were classified as green (meaning that there was enough and strong evidence to support such interventions in CP), mostly applied to children and young people with spastic CP, the majority unilateral (spastic) CP (69). When reviewing the studies mentioned in Novak's systematic review on bimanual training, constrained induced movement therapy, context-focused therapy and goal-directed training, all studies either mentioned that the inclusion criteria was spastic CP or did not mention whether they included dyskinetic CP, nor did they analyse this subgroup of patients separately. Only one study for goal-directed training (home programmes) by Novak et al. 2009 included 5 children with dyskinetic CP from a total of n=36 (134). Whilst this is encouraging, the study had 3 arms for intervention (i) 8 week occupational therapy home

programme (OTHP), ii) 4 weeks OTHP and iii) No OTHP). Due to the small number of dyskinetic CP, randomisation only took place to the 4week OTHP and no OTHP and no children with dyskinetic CP in the 8week OTHP. We acknowledge that stratifying by phenotype would have been difficult with such small percentage of children and young people with dyskinetic CP.

This is also the case for *childhood stroke* and as Ganesan (2013) points out, current rehab approaches are rarely evidence-based and based usually on children with spastic CP (135). Ganesan urges rehab approaches to focus on the pattern of impairment rather than diagnosis, for example dystonia rather than spasticity, which is more likely after arterial ischemic stroke in children. Yet again, most stroke rehabilitation approaches target spasticity. The literature on hemiparesis following *perinatal stroke* is altogether different, partly based on early recognition it has been possible to develop population-based interventional studies of CMT and HABIT alone or combined with transcutaneous Direct Current Stimulation (tDCS) in the state of Alberta, Canada, and this clinical-epidemiological/population-developmental neurobiological multidisciplinary model, along with the background scientific literature has been extensively reviewed by Adam Kirton (136).

A subsequent literature search was performed using the terms ‘dystonia’ OR ‘hyperkinetic movement disorders’ OR ‘athetosis’ OR ‘dyskinetic cerebral palsy’ AND ‘rehabilitation’ OR ‘occupational therapy’ OR ‘physiotherapy’ OR ‘goal-oriented intervention’ OR ‘behavioural intervention’ AND ‘children’ OR ‘childhood’ in order to capture any results from interventions since the published systematic review of systematic reviews by Novak et al. 2013 (69). The results did not show any other pattern in terms of the available reports, mainly including studies developed for inclusion of children with spastic CP.

Despite the absence of clear evidence supporting their use, some authors report on the desirability of frequent of physiotherapy and occupational therapy sessions to be delivered

(137) though this is not based in actual evidence-supported studies. A recent review paper on current and emerging strategies for children with dystonia outlines current intervention strategies, though these again are not based on evidence (92).

### **Is there a role for biofeedback interventions in childhood dystonia?**

Biofeedback in childhood dystonia may be volunteered as useful for learning though this is not based on learning for every day activities and it relates purely to lab based learning studies (88, 92). Interestingly the authors make an assumption that sensorimotor impairments in childhood dystonia hamper acquisition and consolidation of gross and fine motor skills crucial for cognitive and social development. However, it could be debated that these paradigms have not yet been tested since very few if any studies look at the relationship between sensorimotor impairments and acquisition and consolidation of such impairments.

Casellato and colleagues describe two studies in 2012 and 2013 (138, 139) exclusively with children with primary dystonia to improve motor control with EMG-based visual-haptic biofeedback (138) and with error enhancing robot therapy (139). Again, reporting only at the impairment level makes any generalisation to real life situations doubtfully meaningful and conclusions cannot be drawn on whether those changes are in fact clinically significant for the child/young person or in terms of their ability to learn new activities. In our experience, children with primary dystonia continue to have difficulties with day-to-day activities even when dystonia severity is reduced significantly (22) given their non-motor co-morbidities. Therefore motor-learning based approaches might have to include elements beyond sensorimotor rehabilitation or robot generated deviating forces.

### **Ongoing registered trials on childhood dystonia**

On a review of the International Standard Randomised Controlled Trials Number Registry (ISRCTN) we only found 1 study currently in progress. The study is led by the first author of this manuscript (Gimeno, H) and registered ISRCTN57997252 investigating the role of a cognitive-based approach in childhood onset and other HMD using two consecutive series of

N-of-1 trials (140). We are aware of one other pilot study using eye gaze technology with young children with dyskinetic CP but this is not registered and is currently underway (personal communication with Petra Karlsoon, June 2016).

Recommendations for future research are outlined in the last section of this manuscript with proposals about potential designs to improve our understanding and knowledge of childhood dystonia and outcomes.

### **3. Recommendations for multi-centre collaboration in regards to functional clinical outcomes and future research methods**

Primary and secondary dystonia might have more in common than comparisons or extrapolated recommendations from spastic CP studies to dystonia. This follows the saying: ‘dystonia, is dystonia, is dystonia’ regardless of aetiology, so the important strategy is to build on existing models of dystonia.

Given the progress with genetics (*see Silveira-Moryama and Lin 2015 for further discussion*) (9) children with a diagnosis of CP may later on be diagnosed with genetic diagnoses such as dopa-responsive dystonia (DRD), other monogenetic dystonias such as benign hereditary chorea or even an NBIA (9) but new genes, possibly more common than those currently reported are also emerging so we should therefore develop interventions that can work across different aetiological groups in dystonia and other HMD, looking at shared features amenable to intervention as well as specific differences such as timing of onset and the impact of the proportion of life lived with dystonia at a time-critical period of early motor development (65).

We propose below some points to initiate discussion and suggestions for future collaboration.

#### **Suggestions for the future:**

##### **1. Validation of outcome measures:**



Having a non-homogeneous group of young people presents challenges throughout any management strategy implementation such as DBS neuromodulation. Given the limited psychometric testing in well-known outcome measures in CP, which have been mainly tested in spastic CP, we urge caution when applied to childhood dystonia and other HMD.

Ideally, collaborative work between centres that have experience in applying outcome measures with dystonia should be a priority in terms of validating these measures. This requires incorporation of allied health professionals as core members of the multidisciplinary team.

## **2. Allied Health Professionals embedded in multidisciplinary teams:**

It is our impression that there are limited clinical services with bespoke multidisciplinary team approaches to assessment and management of children with movement disorders and this might be a reason for a lack of reports addressing domains of the ICF beyond impairment. Hence, our limited knowledge about effective interventions in domains of activity and participation in the paediatric population, particularly secondary dystonias. It will therefore be difficult to anticipate possible outcomes and establish realistic goals with young people and families. We would encourage multidisciplinary teams to include not only physiotherapy but also occupational therapy, speech and language therapy and psychology colleagues. One proposal will be to join forces in describing goal-acquisition with current available studies in DBS and ITB measured with COPM and GAS. We acknowledge that intense training and work across disciplines in the initial period with professionals working often outside their specific therapy/medical roles will be needed. Ideally, a training package agreed by international consensus (including AHPs) might be a way forward.

## **3. Applying dystonia severity scales:**

Most often international teams focus on impairment with use of dystonia rating scales, which is undoubtedly an important area to describe. Given the heterogeneity of our groups and the difficulties applying a well-established and internationally used outcome measure such as the

BFMDRS to a population with severe disability (above 100 out of 120 in BFMDRS) we propose, as a minimum, that studies report not only a dystonia severity scale but also functional ability classification systems, the GMFCS at a minimum but ideally together with the MACS and CFCS.

#### **4. Capturing the variability in dystonia:**

Variability of performance is characteristic in childhood dystonia and other HMD. Often described as variability within the same hour, day or week, the importance of multiple baselines before intervention may be warranted in this population. Randomised controlled trials, though considered the gold standard, might not be appropriate for these children and young people as a single data point before and after intervention will fail to capture real life performance (i.e. Variability). A potential goal for intervention could be in fact to reduce such a prominent variability, so that performance becomes more stable which in turn might give children and young people more confidence to try new things.

#### **5. Research design in childhood dystonia and other HMD:**

We have outlined the limited evidence and research in childhood dystonia. Mink 2013 highlights how most dystonia ‘treatments’ are designed for and tested in primary dystonia and the ability to generalize these findings for dyskinetic CP or any other form of secondary dystonia is limited (76). We agree that there continues to be an increasing need for further experimental therapeutic research in this population.

Recommendations to consider methodological approaches using proof of principle and pilot studies to allow for subsequent well-designed randomised, controlled trials, and long-term observational trials have been made (6, 76, 141). The use of single-case experimental design or N-of-1 trials using multiple replications across subjects could offer an answer to some of the problems with variability and methodological issues.

## Conclusions:

We present a comprehensive scheme for approaching movement disorders in children, including dystonia and choreoathetosis of necessity originating from many disparate aetiologies. Searching for common themes has helped us as a clinical group, to define core issues relating to refinement of the phenotype with neurophysiological (62, 142), radiological (63, 143, 144) and functional metabolic (145) assessments respectively. These approaches help us understand the physiological context of dystonia and contribute to patient-selection for DBS and also allow interpretation of outcomes, which further refines the selection iteration process. Goal-focussed practices confer an understanding of meaningful outcomes, which in turn result in contented children and families. However past goals must be replaced by future objectives. The dynamic needs of the child, young person, families and carers constitutes the need to incorporate ‘resilient’ assessments, and perhaps more importantly resilient perspectives among referring and treating clinicians, children, young people, device manufacturers and the health-care providers. Neuromodulation for dystonia in children is now at last becoming accepted as a rich, legitimate field of clinical practice which demands as never before a multidisciplinary clinical-research approach to drive our clinical models towards desirable ‘virtuous outcome spirals’ in which each iteration leads to improved function, activity and participation. This and many other contributions to this special edition on Advances in Neuromodulation in Children indicate that although there are no ‘quick fixes’ the prospect for lasting meaningful benefits in chronic, disabling dystonias of childhood are a tangible reality. The challenges of patient stratification for precision medicine-in this case functional neuromodulation neurosurgery- must be grasped wisely.

The lack of studies in childhood dystonia across any intervention other than pharmacological or neurosurgical approaches, which themselves often fail to capture what matters most to children and their carers (5), calls for immediate action from the clinical-scientific community to generate new knowledge on interventions that might be possible with this group of patients. This might require a paradigm shift and the application of knowledge of motor control and

motor learning theories, together with learning and cognitive paradigms to improve outcomes for children and young people with dystonia and other HMD.

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ACCEPTED MANUSCRIPT

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**Highlights:**

A comprehensive scheme for approaching movement disorders in children, including dystonias and choreoathetosis of heterogeneous aetiology is presented.

Searching for common themes helps to define core issues relating to refinement of the phenotype with neurophysiological, radiological and functional metabolic assessments respectively.

These approaches help selection for DBS and also allow interpretation of outcomes, which further refines the selection iteration process.

Goal-focussed practices confer an understanding of meaningful outcomes, which in turn result in contented children and families.

The dynamic needs of the child, families and carers constitutes the need to incorporate 'resilient' assessments, and perhaps more importantly resilient perspectives among referring and treating clinicians, children, young people, device manufacturers and the health-care providers.